II. REMARKS

Claims 53 to 93 are pending in the subject application. Claims 53 to 93 have been examined and stand variously rejected. By this amendment and response, claim 62 has been canceled without prejudice or disclaimer. The abstract and claims 53-59, 65, 71-74, 77, 78, and 80 to 82, have been amended to overcome the Office's objections and rejections. No new matter has been added by these amendments and entry thereof is respectfully requested.

In view of the preceding amendments and the remarks which follow, reconsideration and withdrawal of the rejection is respectfully requested.

Information Disclosure Statement

Applicants respectfully request consideration and entry of the Information Disclosure Statement filed August 6, 2004.

Specification

The Abstract of the Disclosure was objected to because it allegedly was not in standard US PTO format. The Office required correction. Applicants have amended the specification by providing a substitute Abstract as requested by the Office. In view of this amendment, reconsideration and withdrawal of the objection is respectfully requested.

The Office also remarked that the application contains sequence disclosures encompassed by 37 C.F.R. § 1.821(a)(l) and (a)(2). The Office objected to the sequence listing because it allegedly fails to comply with the requirements of 37 C.F.R. § 1.821 through § 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicants have attached hereto an electronic copy of the sequence listing and have requested insertion of a paper copy of same into the application. The paper copy of the Sequence Listing is identical to the copy recorded on the diskette file herewith.

In view of these amendments, submission and remarks, reconsideration and withdrawal of the objection is respectfully requested.

The Office also objected to the disclosure of the following informalities:

The first paragraph at page 1 added by amendment is objected to as allegedly incomplete for failing to specify that the instant case is also a continuation of a PCT application (PCT/US00/20008, filed 07/21/00). Applicant was also respectfully requested to update the information concerning the filing date, patent number and issue date associated with parent case 09/856,127.

In response to the Office's Objection, the specification has been corrected as requested by the Office.

In the experimental section, the Office noted that the technical prefix -- deoxy -- is frequently misspelled "dexoy" in chemical names in titles and in the text. See page 51, line 19; page 52, lines 15 and 26; page 53 at lines 4, 5 and 19; etc. In the disclosure at page 56, the Office noted that the title at lines 2-3 is missing the letter "o" in five separate locations. The Office also noted that the list of numbers and acronym in the left column at page 68 only refers to two identifiable compounds, BVDU (bromovinyldeoxyuridine) and NB 1011 (see page 56, Example 15). Identification of the remainder of the numbers was requested. The structures identified at pages 43 and 44 as was objected to on the ground that either propargylic or allylic moieties are misleading because the three structures shown with substituent formulas specify C_3H_2 (propargylic), but not C_3H_5 (allylic).

To the best of Applicants' ability, the specification has been amended in this Reply to overcome these grounds for rejection. With respect to the list of numbers and acronym in the left column at page 68, these structures are identified on pages 26 and 27 of Applicants' specification. With respect to the rejection regarding the structures appearing on pages 43 and 44, Applicants respectfully request further information regarding this rejection as this is the first objection and/or rejection to the specification on these grounds even though the

terms have been presented in other applications (see, for example, the double patenting rejections set forth by the Office *infra*.)

In view of the preceding amendments and remarks, reconsideration and withdrawal of the objections is respectfully requested.

35 U.S.C. § 101

Claim 62 stands rejected under 35 U.S.C. § 101 allegedly because the claimed recitation of a use, without setting form any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. § 101. In response to the rejection, the claim has been canceled thereby removing the grounds for rejection.

35 U.S.C. § 112, First Paragraph

Claims 59-61 and 87-93 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Office argued that the claims do not meet the written description standard of *Regents of the University of California v. Eli Lilly*, 119 F.3d 1559, 1568; 43 USPQ2d 1398, 1406 (Fed. Cir. 1997).

Applicants respectfully traverse. The subject matter of the claims is directed to chemical compounds and their use in therapeutic or diagnostic methods. In order to satisfy the written description requirement for generic claims involving chemical materials, it is generally accepted that the generic formula (e.g., see Applicants' generic claim 53) must only indicate with specificity what the generic claims cover so that one skilled in the art can identify many of the species that the claims encompass. In contrast, the subject matter under

consideration by the court in the case cited by the Office was directed to nucleic acids, not chemical compounds. Genetic materials differ from chemical compounds in that "a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA' does not distinguish the claimed genus from others except by function, does not specifically define any of the genes that fall within its definition, and does not define any structural features possessed by members of the genus that distinguish them from others." *Id.* at 1568. Applicants' claims are not directed to nucleic acid compounds.

A case factually more similar to the claims under examination is *In re Smythe*, 480 F.2d 1376, 178 U.S.P.Q. 279 (C.C.P.A. 1973). In this decision, the Court held that in spite of a narrow disclosure, an applicant might nonetheless have written description support for a broader claim if the function and properties of what the applicant disclosed in light of the state of the art indicates to those skilled in the art that the invention is indeed broader.

The invention in *Smythe* related to a blood analyzing machine described as a "continuous, automatic analysis system wherein discrete liquid samples . . . are successively introduced into an apparatus as a continuous stream, the individual samples being separated by a segmentizing medium." *Id.* at 1377, 178 U.S.P.Q. at 280. The specification disclosed that the segmentizing medium was an inert gas such as air. The air had to perform the following functions: clean the walls of tubing as it passed; conform to the shape of the tubing to form a barrier; and resist changes in shape when compressed.

Later, Smythe decided to claim inert *fluid*, because the best medium turned out to be liquid. The USPTO rejected the claims, *inter alia*, under the written description requirement of § 112, contending there was nothing in the specification to suggest that Smythe was in possession of these devices with liquid.

The CCPA began its analysis by rejecting the proposition that where the description of the invention in the specification is narrower than in the claim, there has been a failure to comply with the written description requirement. The question was not whether the description is literally there; the question rather is what is conveyed to one having ordinary skill in the art reading the specification. The court observed that the essential functions of the

segmentizing medium are to clean out the tubes as it goes through, to separate these two materials, to take on the shape of the tube, and to resist changes in volume. To the CCPA these functions clearly defined a fluid. One of ordinary skill in the art reading Smythe's disclosure in light of the functions and properties that are performed by what is described would naturally envision the broader content. In the court's view, the person of ordinary skill would realize that Smythe was in possession of the broader concept of using an inert fluid including fluids generally.

Noting that the case before it was not one characterized by unpredictability, the court pointed out that the prior art suggested that liquids, fluids, and gases were equivalent in similar devices. The court went on to give a now-famous hypothetical:

> "If the original specification of a patent application on the scales of justice disclosed only a 1-pound "*lead* weight" as a counterbalance to determine the weight of a pound of flesh, we do not believe the applicant should be prevented, by the so-called "description requirement" of the first paragraph of § 112, or the prohibition against new matter of § 132, from later claiming the counterbalance as a "metal weight" or simply as a 1-pound "weight," although both "metal weight" and "weight" would indeed be progressively broader than "lead weight," including even such an undisclosed, but obviously art-recognized equivalent, "weight" as a pound of feathers. The broader claim language would be permitted because the *description of the use and function* of the lead weight as a scale counterbalance in the *whole disclosure* would immediately convey to any person skilled in the scale art the knowledge that the applicant invented a scale with a 1-pound counterbalance weight, regardless of its composition."

In re Smythe, 480 F.2d at 1384, 178 U.S.P.Q. at 285.

In view of the above, Applicants maintain that the subject specification, when viewed by one of skill in the art, satisfies the written description requirement of 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of the rejection is respectfully requested.

With respect to claims 59-61 and 63-93, the Office argued that the breadth of the claims extends to compounds the synthesis of which has not been defined in a manner

permitting one of ordinary skill to know the identity of the compounds which have shown activity in the treatment of neoplastic disease conditions. Generally, the Office alleged that the specification fails to enable the scope of the claims. The Office specifically argued that:

> "the claim **63** identifies compounds the synthesis and biological testing of which has not been disclosed, including
>
> i) wherein R^1 is C1, I or CN,
>
> ii) wherein R^7 is a ... phosphodiester group or a phosphoramidite group, and
>
> iii) wherein the compound may be in any enantiomeric, diastereoisomeric or stereoisomeric form, including ... L-form α-anomeric form.
>
> In addition, applicant has not supplied any data to support the extension of treatments to include liver cancer.
>
> B. The nature of the invention is directed to 5-substituted-2'-deoxyuridines and analogues thereof as defined by claims 53 and 64, pharmaceutical compositions thereof, a method of testing for relative antineoplastic activity, and method of treating several different neoplastic disease conditions.
>
> C. The state of the prior art is well established by the extensive lists of prior art patents and other references disclosed by the patents issued to Shepard and Shepard et al. listed on the instant PTO-892.
>
> D. The level of one or ordinary skill is high because the practice of the invention requires knowledge of both the organic synthesis of nucleoside analogues and the medical knowledge and training required to properly administer and monitor antineoplastic agents to a host in need thereof.
>
> E. The level of predictability in the art is limited because the number of compounds actually synthesized and/or tested, and the specific disease conditions tested, is very small when compared with the number of compounds included within the scope of the instant claims. In view of the lack complete test data, it is also unclear that the substitution of "C1," "I" or particularly the pseudohalogen "CN for "Br" as an X-substituent will produce equivalent biological testing results. Similarly, most of the variations provided for by the alternatives within the definitions of variables R^6 and R^7 have neither been synthesized nor tested for biological activity. And, only three neoplastic cell types have been shown to be effectively inhibited. For this reason examiner concludes that the asserted and claimed extrapolation to the effective treatment of all "pathological" cell types is not predictable and therefore not adequately enabled.

F. The amount of direction provided by the inventor is difficult to determine because of incomplete synthetic information and incomplete identifying information concerning the identity of compounds tested for biological activity at page 68. Applicant has not provided enabling support for the synthesis of "any enantiomeric, diastereomeric of stereoisomeric form," and in particular has not shown how to make the L-forms and the α-anomers of any of the claimed compounds, or shown that the asserted and claimed pharmaceutical activity of claims 59-61 and 87-93 extends to all possible enantiomers and diastereomers of the compounds defined by claims 53 and 63.

G. The existence of working examples is difficult to determine because of incomplete identifying information concerning either the synthesis of many of the compounds claimed or the identity of compounds tested for biological activity at page 68.

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure is deemed to be excessive in light of the very limited biological test results and synthetic instructions provided for the compounds defined by claims 53 and 63. In particular, the instant method of treatment claims are only enabled for the treatment of one variety of breast cancer, one variety of colon carcinoma, and one fibrosarcoma (HT 1080; organ apparently not specified in the disclosure) according to the table at page 68. There are no enabling examples for the claimed method of testing. Therefore, the Examiner concluded that the amount of experimentation required to practice all aspects of the instant claimed invention is undue."

Applicants respectfully traverse on the ground that the Office has failed to establish a *prima facie* case that the specification does not enable the full scope of the claims. By law a patent application is presumptively enabled when filed. It is incumbent upon the Patent Office, whenever a rejection on grounds of enablement is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. As pointed out by the USPTO in the Section 112 Enablement Training Manual "the case law makes clear that properly reasoned and supported statements explaining any failure to comply with section 112 are a requirement to support a rejection."

Claims 65-66, 71-74, 77-78 and 81-82 also were objected to for lacking terminal punctuation. Applicants have accordingly corrected the foregoing claims to remove this ground for objection and rejection.

In view of the preceding amendments and remarks, reconsideration and withdrawal of the rejections of the claims under 35 U.S.C. § 112, first paragraph, is respectfully requested.

35 U.S.C. § 112, Second Paragraph

Claims 54-59, 63 and 86 stand rejected under 35 U.S.C. § 112, second paragraph, for various reasons of record. For example, claim 54 was indefinite because the term "comprised of a mixture of the E and Z isomers" is allegedly misleading. The Examiner also objected to the subject matter of claim 53 because the words of the claim do not specifically define with "E" or "Z" the stereochemistry of either one of the double bonds in the 5-substituent, or provide for both possibilities for the double bond closest to the uracil ring.

The term "salt" in claims 55 and 56 was objected to because it implies that there is only a single "pharmaceutically acceptable salt without identifying that particular compound.

The term "A composition" in claims 58 and 86, was alleged to be incomplete in light of the subsequent term "pharmaceutically acceptable carrier" and subject matter of claims 59-61 and 91-93, respectively.

The term "the compound" in claims 57, 58 and 59 is alleged to be literally incorrect because each of claims 53-56 is clearly directed to more than a single compound.

The terms "phosphodiester group" and "phosphoramidate group" in claim 63 are alleged to be indefinite because each fails to be defined in sufficient detail to permit the ordinary practitioner to determine the structural metes and bounds of the claimed subject matter.

Applicants have amended the claims in a sincere effort to overcome the grounds for rejection. In view of these amendments, reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Double Patenting

Claims 55 and 56 were rejected under 35 U.S.C. § 101 for allegedly claiming the same invention as that of claims 3 and 4 of prior U.S. Patent No. 6,683,061 (PTO-892 ref. AB). This is a double patenting rejection.

Claims 53-54, 57-86 and 91-93 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-2 and 5-10 of U.S. Patent No. 6,683,061 (PTO-892 ref. AB).

Claims 53-86 and 91-93 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-6 and 28-30 of copending Application Serial No. 10/119,927.

Claims 53-86 and 91-93 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 56, 57 and 61 of copending Application Serial No. 09/782,721.

Claims 60-62 and 87-93 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1 and 20 of copending Application Serial No. 10/051,320 (PTO-892 ref. P3).

The Office also remarked that some or all of claims 53-93 of this application are alleged to conflict with claims 1-6 and 28-30 of copending Application Serial No. 10/119,927, claims 56, 57 and 61 of copending Application Serial No. 09/782,721, and claims 1 and 20 of copending Application Serial No. 10/051,320.

Applicants respectfully defer responding to the above noted rejections until allowable subject matter has been indicated by the Office in the subject application.

III. CONCLUSION

No fee, other than fee for the Three Month Extension of Time is considered necessary in connection with the filing of this Amendment and Reply. However, should the Patent Office determine that additional relief is required, Applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such

petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 50-2518**, referencing attorney docket no. 2023896-7008307001. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

If telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (650) 849-4950.

Respectfully submitted,

Date: Sept. 15, 2004

By: _____
Antoinette F. Konski
Registration No.: 34,202

Bingham McCutchen LLP
Three Embarcadero Center
San Francisco, California 94111
Telephone: (415) 393-2000
Telefax: (415) 393-2286